Journal of Interventional Medicine 2 (2019) 1–4

HOSTED BY

ELSEVIER

Contents lists available at ScienceDirect

Journal of Interventional Medicine

journal homepage: www.keaipublishing.com/cn/journals/journal-of-interventional-medicine/

Radiation segmentectomy for hepatic malignancies: Indications, devices, dosimetry, procedure, clinical outcomes, and toxicity of yttrium-90 microspheres

Zhongzhi Jia [a,b], Caoye Wang [c], Ricardo Paz-Fumagalli [d], Weiping Wang [d,*]

[a] Department of Interventional Radiology, Second People's Hospital of Changzhou, Changzhou, 213003, China
[b] The Center of Medical Physics with Nanjing Medical University, Changzhou, 213003, China
[c] Department of Interventional Radiology, First People's Hospital of Changzhou, Changzhou, 213000, China
[d] Department of Radiology, Mayo Clinic, Jacksonville, FL, 32224, USA

ARTICLE INFO

Keywords:
Hepatic malignancy
Yttrium-90
Radioembolization
Radiation segmentectomy

ABSTRACT

Radiation segmentectomy (RS) is a new approach to ^{90}Y radioembolization that has been designed to increase the safety and efficacy of radioembolization in patients with unresectable hepatic malignancies. With this technique, high doses (>190 Gy) of radiation are delivered to the tumor through radioembolization performed in a segmental fashion, potentially increasing the radiation dose to the tumor while minimizing injury to the liver parenchyma. The aim of this review is to provide a summary of the indications, device choice, dosimetry, procedure, clinical outcomes, and toxicity of RS based on the clinical series currently available.

1. Introduction

Radiation segmentectomy (RS) with yttrium-90 (^{90}Y) radioembolization for unresectable hepatic malignancies was developed to increase the radiation dose to the target tumor while minimizing injury to the liver parenchyma.[1–3] By limiting the perfusion area of ^{90}Y microspheres to liver parenchyma in no more than 2 hepatic segments,[3] this technique can achieve a high radiation dose (>190 Gy) to the tumor-containing hepatic segments.[4] Preliminary reports have shown that this technique is safe and effective in the management of hepatic malignancies.[3,5,6] The purpose of this review is to provide an overview of the indications, device choice, dosimetry, procedure, clinical outcomes, and toxicity of RS based on the clinical series available to date.

2. Indications

Patients eligible for RS therapy are those with 1) a solitary tumor ≤5 cm (primary or secondary liver tumor); 2) liver-only disease (primary liver tumor without extrahepatic metastasis or secondary liver tumor without other organ metastasis); and 3) a tumor that can be isolated angiographically such that no more than 2 hepatic segments are perfused during treatment.[4]

3. Embolic devices

Two microsphere devices are commercially available: TheraSphere (glass, British Technology Group, UK) and SIR-Spheres (resin, Sirtex Medical, Australia).[7] TheraSphere is the only microsphere device that has been used for RS because its activity per microsphere is higher than that of SIR-Spheres (2500 Bq vs 50 Bq).[4,6,8,9] The small particulate volume of these glass microsphere doses allows for superselective small-volume, high-radiation administration while reducing the risk of vascular occlusion/stasis and incomplete administration.

4. Dosimetry

Calculating the correct dose for RS is critical; however, no consensus has been reached regarding how to best calculate doses for this procedure. Salem et al.,[3] who were the first researchers to propose the concept of RS, calculated dose based on the mass of the lobe receiving radiation. Biederman et al.[10] also reported dosimetry based on lobar volumes, even though all of the radiation particles were delivered to a segmental artery.

In general, radiation dosimetry in radioembolization is calculated primarily based on the assumption that microspheres will be distributed uniformly between the tumor and the normal parenchyma (Table 1; Fig. 1).[11] However, this approach has obvious limitations, as the blood

* Corresponding author. Department of Radiology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL, 32224, USA.
E-mail address: wang.weiping@mayo.edu (W. Wang).

https://doi.org/10.1016/j.jimed.2019.05.001

Available online 12 May 2019

supply to the tumor is predominantly from the hepatic artery, whereas the liver parenchyma is primarily perfused by the portal vein.[12] Therefore, relative hepatic arterial hyperperfusion should be considered as an important factor in dosimetry calculations for radioembolization. With this technique, the tumor is assigned a hypervascularity ratio relative to the surrounding perfused parenchyma according to the subjective assessment of an interventional radiologist who has reviewed the results of an angiogram, a contrast-enhanced cross-sectional imaging study (computed tomography or magnetic resonance imaging), and a technetium-99 m macroaggregated albumin (99mTc-MAA) scan. This ratio ranges from 1 to 10, with a value of 1 representing a tumor with the same vascularity as the surrounding parenchyma and a value of 10 representing a tumor receiving 100% of the blood flowing to the tumor. Doses delivered to the tumor and normal parenchyma are then calculated as follows: 1) dose to tumor: $D_{ST} = 50\ (A)\ (1–LSF)\ (1–R)\ (P_T)/M_T$; and 2) dose to normal parenchyma: $D_{SN} = 50\ (A)\ (1–LSF)\ (1–R)\ (1–P_T)/(M_S–M_T)$, where D_{SN} and D_{ST} are the doses delivered to the mass of infused normal parenchyma ($M_S–M_T$) and tumor (M_T) upon segmental infusion, A is the administered activity in GBq, LSF is the lung shunt fraction, R is the fraction of activity remaining in the vial, and P_T is the percentage of the microspheres delivered to the tumor (calculated from the hypervascularity ratio). Recent research has demonstrated that with the use of cone-beam computed tomography, the perfused volume (and hence mass) can now be measured during mapping angiography, resulting in more accurate dosimetry planning for RS. With this method, the total radiation dose used during RS is reduced when compared with the dose used during whole or lobar ^{90}Y radioembolization, but the radiation dose delivered to the tumor is high.[3]

5. Procedure

The RS procedure follows the procedure established by general consensus for ^{90}Y radioembolization therapy.[3,8] All patients undergo mapping angiogram so that the operator can 1) determine the vascular anatomy of the region, 2) identify the vascular supply of the tumor, 3) prophylactically embolize vessels that may lead to nontarget deposition of microspheres, and 4) perform 99mTc-MAA scans to determine LSF and splanchnic shunting. The feeding vessel of the segment(s) targeted for treatment is then identified and catheterized. The key to successful RS is to catheterize the target arterial territory as selectively as possible, including the entire tumor and excluding as much normal liver as possible, as this will increase efficacy while decreasing risk.

6. Clinical outcomes and toxicity

To assess the clinical outcomes and toxicity of RS in the management of hepatic malignancies, we conducted a systematic search of the literature. The PubMed database was searched for studies describing RS published between January 1, 1991 (introduction of first commercially available ^{90}Y product) and June 2018, using the keywords “radiation segmentectomy,” or “radiation lobectomy,” and “English language.” Review articles, animal studies, laboratory investigations, case reports, and duplicated clinical studies were excluded. A total of 4 retrospective clinical studies were identified through this search. From these studies, a total of 155 cases, including 145 cases of hepatocellular carcinoma (HCC) and 10 cases of hepatic metastases (colorectal cancer, n = 7; breast cancer, n = 1; leiomyosarcoma, n = 1; carcinoid tumor, n = 1), were included in the final analysis (Table 2). Glass microspheres were used in all patients. Of note, 12 cases with segmental portal vein tumor thrombus were included in 1 study.[14]

Table 1
Calculation of radiation dose.

Infusion location	Radiation dose
Proper hepatic artery	$D_W = 50\ (A)\ (1–LSF)\ (1–R)/M_W$
Lobar artery	$D_L = 50\ (A)\ (1–LSF)\ (1–R)/M_L$
Segmental artery	$D_S = 50\ (A)\ (1–LSF)\ (1–R)/M_S$
Tumor artery	$D_T = 50\ (A)\ (1–LSF)\ (1–R)/M_T$

D_W, D_L, D_S, and D_T are the doses delivered to masses of the whole liver (M_W), lobe (M_L), segment (M_S), and tumor (M_T), respectively (see Fig. 1). A is the administered activity in GBq, LSF is lung shunt fraction, and R is the fraction of activity remaining in the vial. M is the mass of the tissue perfused by the microspheres in kilograms. M is determined after converting the volume of the tissue to kilograms using the conversion factor of 1.03×10^{-3}kg/cm^{-3}.[13]

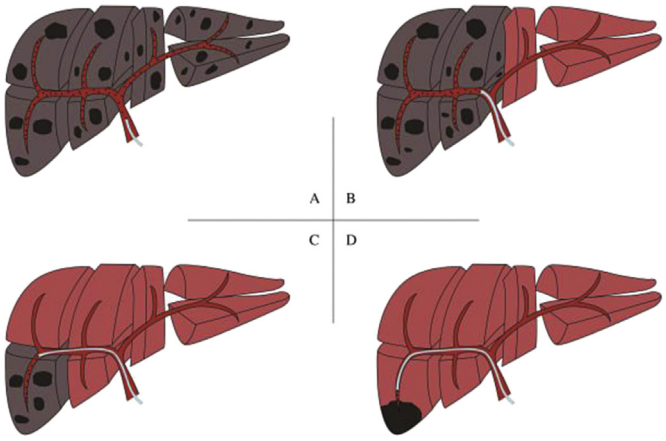

Fig. 1. Various assumptions of infusion locations. (A) Multifocal bilobar hepatocellular carcinoma (HCC) with whole-liver infusion. (B) Multifocal unilobar HCC with lobar infusion. (C) Multifocal HCC confined to ≤2 hepatic segments with segmental infusion. (d) Solitary HCC with infusion of tumor only.

Table 3 summarizes the clinical outcomes of RS with respect to tumor response, time to progression (TTP), progression-free survival (PFS), and overall survival (OS). The tumor response at 3 or 6 months was reported for all patients, with a complete response (CR) rate ranging from 20% to 81.8%, a partial response (PR) rate ranging from 10% to 70%, a stable disease (SD) rate ranging from 1.8% to 40%, and a progressive disease (PD) rate ranging from 0% to 8%. The disease control rates ranged from 92% to 100%. Two out of 4 studies reported the median TTP (10.6 and 28.8 months),[6,14] and a median PFS of 7.1 months was reported in 1 study.[5] The OS was reported in 2 studies (37.6 and 80.4 months).[6,10] One-year survival rates of 86.5% and 98% were reported in 2 studies,[6,14] and 1 study reported 3- and 5-year survival rates of 66% and 57%, respectively.[6]

Among the patients enrolled in the 4 studies, only 1 patient developed rapidly progressive disease, exhibiting grade 3 bilirubin and albumin toxicity 3 months after RS and dying 4 months after RS. Grade 3 toxicity was reported in 9 patients, and Grade 1 and 2 toxicity was reported in 11 patients (Table 4).

7. Discussion

Although HCC is a radiosensitive tumor, the use of radiation in patients with HCC has been limited by the risks of nontargeted tissue exposure and radiation injury, as radiation affects both tumor cells and uninvolved normal cells.[15] A typical safe dose (ie, one that does not cause substantial organ damage) of external beam radiation therapy is approximately 30 Gy for the whole liver.[16] However, this dose is likely not high enough to lead to a tumor response.[17] Catheter-based administration of ^{90}Y microspheres into the hepatic artery is thought to preferentially deliver therapy to the tumor, sparing the normal liver parenchyma. This technique allows for locoregional delivery of radiation doses of 80–150 Gy (or even higher).[13]

The response of HCC to radiation therapy is dose dependent. In a group of 158 patients with HCC who were treated with 3D conformal radiotherapy, Park et al.[18] observed response rates of 29.2%, 68.6%, and 77.1% in patients treated with doses <40 Gy, 40–50 Gy, and >50 Gy,

Table 2
Characteristics of study patients undergoing RS therapy in the included studies.

Study	Publication date	No. of cases	Type of malignancy	BCLC stage, no. of cases (A, B, C, D)	Child-Pugh classification, no. of cases (A, B, C)	Median dosage
Lewandowski et al.[6]	2018	70	HCC (solitary tumor ≤5 cm)	70, 0, 0, 0	70, 0, 0	N/A
Biederman et al.[10]	2018	55	HCC (solitary tumor ≤3 cm)	N/A	N/A	D_S: 1.4 Gbq (1.1–2.1)
Meiers et al.[5]	2017	10	Hepatic metastases	N/A	N/A	D_S: 261 Gy
Padia et al.[14]	2014	20	HCC (median, 3.9 cm); 12 cases with segmental portal vein tumor thrombus	2, 2, 15, 1	11, 8, 1	D_S: 255 Gy D_T: 536 Gy

BCLC = Barcelona Clinic Liver Cancer; HCC = hepatocellular carcinoma; N/A = not available; D_S and D_T = doses delivered to masses of the segment and tumor, respectively.

Table 3
Clinical outcomes of RS therapy.

Study	Assessment criteria	Tumor response, % (CR, PR, SD, PD)	Disease control rate, %	Time to progression, mo	Progression-free survival, mo	Overall survival, mo	1-, 3-, 5-year survival, %
Lewandowski et al.[6]	EASL	44, 42, 6, 8 at 6 mo	92 at 6 mo	28.8 (median)	N/A	80.4	98, 66, 57
Biederman et al.[10]	mRECIST	81.8, 10.9, 1.8, 5.5 at 3 mo	94.5 at 3 mo	N/A	N/A	37.6	N/A
Meiers et al.[5]	PERCIST	50, 10, 40, 0 at 3 mo	100 at 3 mo	N/A	7.1	N/A	N/A
Padia et al.[14]	WHO	20, 70, 10, 0 at 1 mo	100 at 3 mo	10.6 (median)	N/A	N/A	86.5, N/A, N/A

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; EASL = European Association for the Study of the Liver; N/A = not available; mRECIST = Modified Response Evaluation Criteria in Solid Tumors; PERCIST = PET Response Criteria in Solid Tumors; WHO = World Health Organization.

respectively. Similar results have been obtained with the use of ^{90}Y microspheres. For instance, Vouche M et al.[8] reported 102 patients with HCC who underwent RS because they were not candidates for surgical resection or radiofrequency ablation. Of these 102 patients, 33 (32.4%) cases underwent liver transplant, and the pathology analysis demonstrated that complete necrosis was more common in patients treated with radiation doses that exceeded 190 Gy than in those exposed to lower doses (66.7% vs 25%; $P = .03$).[8] In the studies included in our analysis, Padia et al.[14] and Riaz et al.[3] reported median doses to the tumor of 536 and 1214 Gy (Table 5), approximately 10 times higher than the tumoricidal dose of 60 Gy.[19]

The purpose of RS, therefore, is to deliver an "ablative" dose to a target area in order to completely destroy the tumor along with the tumor-bearing parenchyma. This is achieved by prospectively determining lobar volumes, prescribing an intended lobar dose (>120–150 Gy), and administering the dose into the feeding vessel(s) to increase safety and minimize radiation to normal parenchyma.

7.1. Imaging response and survival

Limited comparison data exist regarding hepatic imaging response and OS with RS therapy versus other local treatment methods. Only 2 such studies in patients with HCC have been published,[9,10] both conducted by Biederman et al. In the earlier study,[9] the outcomes of RS and transarterial chemoembolization (TACE) combined with microwave ablation (MWA) were compared for the treatment of unresectable solitary HCCs (up to 3 cm) in 80 patients. In this study, the CR rate with RS was comparable to the rate with TACE plus MWA (82.5% [33/40] vs 85.0% [34/40]; $P = .94$). In addition, the TTP with RS was comparable to the TTP with TACE plus MWA (11.1 months vs 11.6 months; $P = .83$). In terms of OS, this study demonstrated no significant difference between the 2 groups ($P > .99$). In a later study,[10] RS was compared with TACE in patients with unresectable solitary HCC lesions (up to 3 cm); for each group, the CR, time to secondary therapy (TTST), and OS were assessed. The CR rate was 92.1% (35/38) for RS and 52.6% (18/38) for TACE (odds ratio, 18.0; 95% confidence interval [CI], 2.41–135; $P = .005$) after propensity score matching was performed. The median (95% CI) TTST after matching was 812 days (363–812 days) in the RS group and 161 days (76–350 days) in the TACE group (95% CI, 0.08–0.55; $P = .001$). The mean OS was not significantly different between the 2 groups (RS, 27.6 months; TACE, 27.4 months; $P = .71$).[10] Therefore, there is no definitive evidence that RS treatment is superior to other locoregional therapies.

Table 4
Summary of complications and side effects in patients undergoing RS therapy.

Study	Complications and side effects
Lewandowski et al.[6]	Grade 3: RILD (n = 3; 4.2%), including 1 patient (1.4%) who developed rapidly progressive disease, exhibited grade 3 RILD at month 3, and died 4 months after RS
Biederman et al.[10]	Grade 3: RILD (n = 6; 11%)
Meiers et al.[5]	Grade 1: Phrenic irritation (n = 1; 10%)
Padia et al.[14]	Grade 1 and 2: Fatigue (n = 6; 30%), abdominal pain (n = 2; 10%), postembolization syndrome (n = 2; 10%)

RILD = radiation-induced liver disease.

7.2. Bridge-to-resection/transplant

RS has demonstrated efficacy in downstaging HCC by achieving local tumor control and is therefore considered a bridging therapy for tumor resection or transplant.[4,10] Biederman et al.[10] reported that 14.5% (8/55) of patients who underwent RS in their study eventually underwent liver transplant. Similarly, Vouche et al.[8] reported that 32% (33/102) of

Table 5
Median doses used during RS therapy.

Study	D_W, Gy	D_L, Gy	D_S, Gy	D_T, Gy
Padia et al.[14]	–	–	254 (105–1055)	536 (203–1618)
Meiers et al.[5]	–	–	261 (119–477)	–
Vouche et al.[8]	–	–	242 (173–369)	–
Riaz et al.[3]	35.5 (32–41.3)	97 (89–110)	521 (404–645)	1214 (961–1546)
Median	35.5	97	257.5	875

D_W, D_L, D_S, and D_T were the doses delivered to masses of the whole liver, lobe, segment, and tumor, respectively.

patients they assessed underwent liver transplant after RS.

RS can lead to volumetric changes of the liver depending on the volume exposed to radiation; the most common outcome is atrophy of the treated volume and compensatory hypertrophy of the rest. This effect can help to identify patients who would benefit most from surgery, thereby improving postoperative outcomes and minimizing recurrence rates.[8] In one study, Vouche et al.[20] reported that right lobe atrophy and left lobe hypertrophy were observed as soon as 1 month after RS, and the median percent of future liver remnant hypertrophy reached 45% after 9 months ($P < .001$). The clinical significance of this finding is that hypertrophy of the normal liver tissue may potentially be of benefit for surgical lobectomy.

7.3. Safety

Of the patients included in this analysis, only 1 case developed rapidly progressive disease, exhibiting grade 3 radiation-induced liver disease 3 months after RS and dying 4 months after RS. All other patients with grade 1 and 2 (7.1%) or grade 3 (5.8%) toxicities were treated conservatively and recovered uneventfully. These results suggest that RS is a generally well-tolerated procedure, underscoring the increased safety that superselective intra-arterial infusion of the ^{90}Y microspheres offers by reducing nontarget liver parenchymal exposure.

8. Limitations

Our analysis of clinical outcomes and safety had several limitations. Only a few studies of RS have been published since the technique was first introduced, and we identified only 4 retrospective studies that were eligible for inclusion in our analysis (ie, included data regarding clinical outcomes and safety). There was no consensus among the studies regarding dosimetry for RS. The 4 studies also varied in their inclusion criteria, doses delivered to masses, and assessment criteria of tumor response, which may have biased the results. Finally, the role of this technique in metastatic liver tumors remains to be determined, as most of the patients included in this analysis had HCC.[5]

9. Conclusions

RS therapy involves superselective administration of Y-90 microspheres to hepatic malignancies. With this technique, a high dose of radiation is delivered to the target tumor and surrounding parenchyma, thus increasing the tumoricidal effect while minimizing side effects. The studies of RS performed to date provide some evidence that RS can achieve these goals. However, the data are limited and further research is needed, particularly prospective studies with large patient populations that include patients with metastatic disease.

Funding sources

This study was supported by the High-Level Medical Talents Training Project of Changzhou (2016CZBJ009). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interest

The authors indicate no potential conflicts of interest.

Acknowledgements

We thank Megan Griffiths, scientific writer, Cleveland, Ohio, USA, and Qiao Chen for their help with revising the manuscript.

References

1. Salem R, Lewandowski RJ, Kulik L, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology*. 2011;140:497–507 e2.
2. Salem R, Lewandowski RJ, Gates VL, et al. Research reporting standards for radioembolization of hepatic malignancies. *J Vasc Interv Radiol*. 2011;22:265–278.
3. Riaz A, Gates VL, Atassi B, et al. Radiation segmentectomy: a novel approach to increase safety and efficacy of radioembolization. *Int J Radiat Oncol Biol Phys*. 2011;79:163–171.
4. Mora RA, Ali R, Gabr A, et al. Pictorial essay: imaging findings following Y90 radiation segmentectomy for hepatocellular carcinoma. *Abdom Radiol (NY)*. 2017;43:1–16.
5. Meiers C, Taylor A, Geller B, et al. Safety and initial efficacy of radiation segmentectomy for the treatment of hepatic metastases. *J Gastrointest Oncol*. 2018;9:311–315.
6. Lewandowski RJ, Gabr A, Abouchaleh N, et al. Radiation segmentectomy: potential curative therapy for early hepatocellular carcinoma. *Radiology*. 2018;287:1050–1058.
7. Murthy R, Nunez R, Szklaruk J, et al. Yttrium-90 microsphere therapy for hepatic malignancy: devices, indications, technical considerations, and potential complications. *Radiographics*. 2005;25:S41–S55.
8. Vouche M, Habib A, Ward TJ, et al. Unresectable solitary hepatocellular carcinoma not amenable to radiofrequency ablation: multicenter radiology-pathology correlation and survival of radiation segmentectomy. *Hepatology*. 2014;60:192–201.
9. Biederman DM, Titano JJ, Bishay VL, et al. Radiation segmentectomy versus TACE combined with microwave ablation for unresectable solitary hepatocellular carcinoma up to 3 cm: a propensity score matching study. *Radiology*. 2017;283:895–905.
10. Biederman DM, Titano JJ, Korff RA, et al. Radiation segmentectomy versus selective chemoembolization in the treatment of early-stage hepatocellular carcinoma. *J Vasc Interv Radiol*. 2018;29:30–37 e2.
11. Rhee TK, Omary RA, Gates V, et al. The effect of catheter-directed CT angiography on yttrium-90 radioembolization treatment of hepatocellular carcinoma. *J Vasc Interv Radiol*. 2005;16:1085–1091.
12. Grady ED, Auda SP, Cheek WV. Vasoconstrictors to improve localization of radioactive microspheres in the treatment of liver cancer. *J Med Assoc Ga*. 1981;70:791–795.
13. Salem R, Thurston KG. Radioembolization with 90Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: technical and methodologic considerations. *J Vasc Interv Radiol*. 2006;17:1251–1278.
14. Padia SA, Kwan SW, Roudsari B, et al. Superselective yttrium-90 radioembolization for hepatocellular carcinoma yields high response rates with minimal toxicity. *J Vasc Interv Radiol*. 2014;25:1067–1073.
15. Feng M, Ben-Josef E. Radiation therapy for hepatocellular carcinoma. *Semin Radiat Oncol*. 2011;21:271–277.
16. Lewandowski RJ, Salem R. Yttrium-90 radioembolization of hepatocellular carcinoma and metastatic disease to the liver. *Semin Intervent Radiol*. 2006;23:64–72.
17. Goin JE, Salem R, Carr BI, et al. Treatment of unresectable hepatocellular carcinoma with intrahepatic yttrium 90 microspheres: factors associated with liver toxicities. *J Vasc Interv Radiol*. 2005;16:205–213.
18. Park HC, Seong J, Han KH, et al. Dose-response relationship in local radiotherapy for hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2002;54:150–155.
19. Bradley J, Hu C. Learning from trials on radiation dose in non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2016;96:748–750.
20. Vouche M, Lewandowski RJ, Atassi R, et al. Radiation lobectomy: time-dependent analysis of future liver remnant volume in unresectable liver cancer as a bridge to resection. *J Hepatol*. 2013;59:1029–1036.